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Accelerated vascular ageing after COVID-19 infection: the CARTESIAN study

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Abstract

Background and Aims Increasing evidence suggests that COVID-19 survivors experience long-term cardiovascular complications possibly through development of vascular damage. The study aimed to investigate whether accelerated vascular ageing occurs after COVID-19 infection, and if so, identify its determinants.

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Methods This prospective, multicentric, cohort study, included 34 centres in 16 countries worldwide, in 4 groups of participants—COVID-19-negative controls (i) and three groups of individuals with recent (6 ± 3 months) exposure to SARS-CoV-2: not hospitalized (ii), hospitalized in general wards (iii), and hospitalized in intensive care units (iv). The main outcome was carotid-femoral pulse wave velocity (PWV), an established biomarker of large artery stiffness.

Results 2390 individuals (age 50 ± 15 years, 49.2% women) were recruited. After adjustment for confounders, all COVID-19-positive groups showed higher PWV (+0.41, +0.37, and +0.40 m/s for groups 2–4, $P < .001$, $P = .001$ and $P = .003$) vs. controls [PWV 7.53 (7.09; 7.97) m/s adjusted mean (95% CI)]. In sex-stratified analyses, PWV differences were significant in women [PWV (+0.55, +0.60, and +1.09 m/s for groups 2–4, $P < .001$ for all)], but not in men. Among COVID-19 positive women, persistent symptoms were associated with higher PWV, regardless of disease severity and cardiovascular confounders [adjusted PWV 7.52 (95% CI 7.09; 7.96) vs. 7.13 (95% CI 6.67; 7.59) m/s, $P < .001$]. A stable or improved PWV after 12 months was found in the COVID+ groups, whereas a progression was observed in the COVID− group.

Conclusions COVID-19 is associated with early vascular ageing in the long term, especially in women.

Structured Graphical Abstract

Key Question

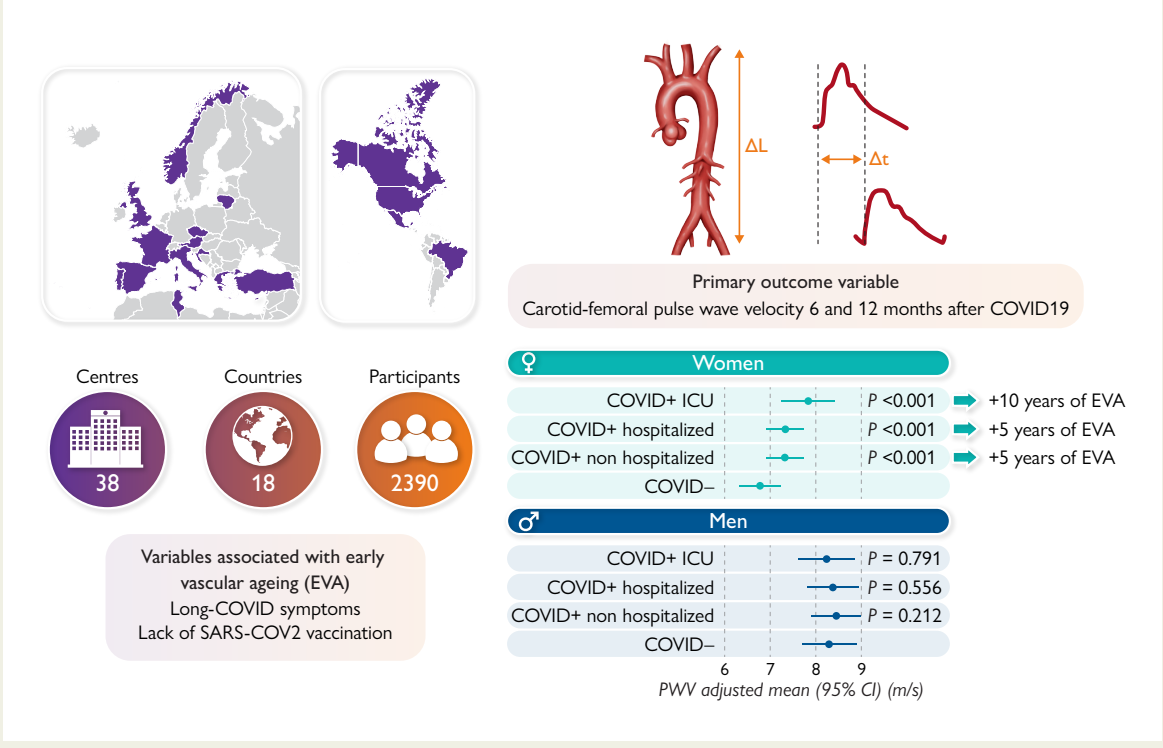
COVID19 survivors may have increased cardiovascular disease risk mediated by early vascular ageing. Is vascular ageing accelerated after COVID19 infection? What are its determinants?

Key Finding

In this multinational study, after adjustment for confounders, COVID19-positive individuals showed higher pulse wave velocity (PWV) as compared to COVID19-negative individuals 6 months after COVID19. In sex-stratified analyses, increased PWV was present in women, but not in men. Early vascular ageing persisted, though attenuated, 12 months after COVID19.

Take Home Message

COVID19 infection is significantly associated with long-term vascular ageing, particularly in women.



COVID-19 effects on ARTErial StIffness and vascular AgeiNg: the CARTESIAN study. CI, COnfidence Intervals; COVID, Corona VIrus Disease; EVA, early vascular ageing; ICU, Intensive Care Unit; PWV, pulse wave velocity; SARS-COV2, Severe acute respiratory syndromecoronavirus 2.

Keywords Arterial stiffness • Long COVID • COVID-19 • Vascular ageing • Sex differences

Introduction

COVID-19 is an unprecedented health emergency that continues to cause death and disease worldwide even after more than 4 years of its first occurrence. Perhaps more alarmingly, according to the World Health Organization, there are currently almost 800 million COVID-19 survivors worldwide who represent a large number of people at risk for long-term complications of COVID. Recent findings show that beyond acute illness, a substantial number of COVID-19 survivors experience a heavy burden of long-lasting health loss,[1] including increased incidence of cardiovascular (CV) disease.[2,3] This has been observed up to 12 months after infection, with a gradient of risk according to the severity of acute COVID-19 infection.[2] Indeed, COVID-19 can be considered a vascular disease,[4] since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affect the vascular system either directly, the virus using angiotensin-converting enzyme 2 (ACE2) as cell entry receptor, or indirectly as a result of elevation of systemic inflammatory cytokines.[5]

Evidence is accumulating regarding long-term CV consequences: Patients with acute myocardial injury during COVID-19 often have persistent cardiac abnormalities, such as fibrosis determined via magnetic resonance imaging in up to 49% of cases[6] and diastolic dysfunction during exercise.[7]

Identifying COVID-19 survivors who will experience long-term CV complications is an unmet need. Susceptible patients are likely to benefit from protective measures, either non-pharmacological or pharmacological. Vascular ageing assessment, for example, by arterial stiffness measurement, improves CV risk stratification and has been demonstrated to correctly reclassify individuals at higher risk categories on top of classical risk factors.[8,9] The concept of vascular ageing, as opposed to chronological ageing, reflects the individual variability in vascular disease onset and mortality[10]; it has demonstrated utility in the assessment of the burden of emerging risk factors for CV disease.[11]

We hypothesized that COVID-19 survivors would experience accelerated vascular ageing, proportional to the severity of the infection.

In this context, we launched the CARTESIAN study (Covid-19 effects on ARTErial StIffness and vascular AgeiNg, NCT04558450)—the first international multicenter study on the long-term effects of COVID-19 on non-invasive biomarkers of vascular ageing.[12] The main objective of the CARTESIAN study was to evaluate the presence of accelerated vascular ageing after COVID-19 infection. The primary end-point was carotid-femoral pulse wave velocity (PWV), an established biomarker of arterial stiffness and vascular ageing.[13]

Methods

The CARTESIAN study is a prospective, multicentre, cohort study. In May 2020, a call for interest was launched through the Artery Society and VascAgeNet members.[14] Finally, 38 centres from 18 countries completed the regulatory steps and contributed to the cohort: the full list of recruiting centres and investigators is provided as an Online Supplement.

The CARTESIAN study was planned as a joint analysis of several national studies, using an identical protocol written by the Cartesian Scientific Committee. Approval by local Ethics Committee was obtained in each centre. Additional studies, with ethical clearance complying with the Declaration of Helsinki and using similar techniques and protocols, were also included in the final analysis of the CARTESIAN study. Each centre signed data transfer agreements with the coordinating centre (PARCC-Inserm, Paris) for anonymized data transfer through an electronic case report form on a secure server (REDCap electronic data capture tool).[15,16] The protocol is registered on ClinicalTrials.gov (NCT04558450). Anonymized data are available for research purposes upon submission of a proposal to the corresponding author and after approval by the CARTESIAN Scientific Committee.

Study population

The study comprised of (i) a control group of individuals who tested negative for SARS-CoV-2 infection and three groups of individuals with recent (6 ± 3 months) documented exposure to SARS-CoV-2; (ii) patients with confirmed infection by SARS-CoV-2, not requiring hospitalisation (symptomatic or not); (iii) patients with confirmed infection by SARS-CoV-2, requiring hospitalisation but not admission to an intensive care unit (ICU); and (iv) patients with confirmed infection by SARS-CoV-2, requiring hospitalisation in an ICU.

Recruitment took place from September 2020 to February 2022, with different modalities across centres, ranging from advertisement to invitation of pre-existing cohort study participants. Since the recruitment was mostly done during early pandemic phases, in some centres negative controls were recruited mostly among hospital staff to minimize infection risk. Written informed consent was obtained from all participants. COVID-19 status was assessed through reverse transcriptase-polymerase chain reaction (RT-PCR), antigen rapid tests, or positive serology for COVID-19 (if the participant was non-vaccinated).

The exclusion criteria were: inability to provide written consent, pregnancy or breastfeeding, diseases carrying out a life expectancy of <1 year according to clinical judgment, arrhythmia or any other circumstance that would preclude full participation in the study according to clinical judgement.

Study design

The detailed study design, with the complete study plan, is described elsewhere.[12] The present paper describes the results of the main outcome variable, PWV, 6 ± 3 months and 12 ± 3 months after COVID-19.

Experimental session

Standard operating procedures were written by the scientific committee and provided to all investigators. Whenever possible, study participants were asked to bring with them medical records (such as hospitalisation reports, blood sample and nasal swab results) concerning COVID-19 and other comorbidities and underwent a structured interview to collect clinical information about previous COVID-19 infection, vaccination status, CV risk factors and treatments, comorbidities. A group of questionnaires for quality of life and psychosocial status for self-administration were also completed. Then, anthropometric parameters were taken, as well as blood pressure (BP) and vascular measurements (PWV in all centres, optional tests in selected centres). A description of questionnaires and optional tests, constituting secondary endpoints of the study, is available in a separate publication.[12]

Brachial BP was measured using a validated device according to the Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organisation for Standardisation (AAMI/ESH/ISO) protocol.[17] Three measurements were performed in the supine position at the non-dominant arm at intervals of 2 min after 10 min of rest before starting the PWV measurement.

Large artery stiffness was assessed by carotid-femoral PWV.[18] Waveforms were recorded at the right femoral and carotid site, using validated devices,[19] such as SphygmoCor (AtCor Medical, Sydney, NSW, Australia), Complior (Alam Medical, Vincennes, France), PulsePen (PulsePen, DiaTecne, Milan, Italy), or Vicorder (80Beats Medical, Berlin, Germany). Briefly, after BP measurement, a probe or cuff was placed on the carotid and femoral artery while 10–15 subsequent heartbeats were recorded, allowing to measure pulse transit time (PTT). PTT values <20 or >130 ms were considered invalid. Three consecutive PTT measurements were performed for each patient. Transit distance was estimated using a population-derived formula obtained from routinely collected clinical information such as age, height, weight, heart rate and sex, which has been shown to be accurate and to reduce intercenter measurement variability without impacting the

diagnostic utility of PWV.[20] PWV was then calculated as the ratio between distance and PTT.[18] Three radial artery waveform acquisitions were also run, in order to measure central BP and augmentation index (AIx).

Statistical analysis

Statistical analysis was performed with R (Version 4.1.2) and Rstudio (Version 1.2.5042). Data cleaning for removing extreme outliers was performed. The following intervals of acceptance for physiological variables were used: age 18–110 years; PWV 3–20 m/s; weight 30–200 kg; height 1.3–2.5 m; brachial and central systolic BP 60–250 mmHg; brachial and central diastolic BP 40–160 mmHg; heart rate 35–200 bpm; AIx −20 to 50%. More in detail, 14 PWV (PTT >130 or <20 ms), 5 weight (>200 kg), 1 systolic BP (<60 mmHg) values were removed because they were considered extreme outliers, possibly attributable to invalid measurements (concerning PWV) or typing errors.

Data are shown as counts and percentages for categorical variables and as mean ± SD and median (25%–75% IQR) for continuous variables. Clinical characteristics of the study population between groups were compared by chi-square (categorical variables) or Kruskal–Wallis test (continuous variables).

In order to take into account of the clustered nature of data in terms of PWV measuring device type used, country income level and modality of recruitment, hierarchical mixed linear regression modelling analysis was performed to compare PWV across the four disease groups, using the R packages nlme and lme4. Device type (categorized as Sphygmocor tonometry device, Sphygmocor oscillometric device and others), country income (categorized as low-middle income country—yes/no) were included as random effect variables. Potential confounders were chosen *a priori* and considered to be: age, sex, body mass index (BMI), smoking, established CV disease, treated hypertension and diabetes; these variables were included in models as fixed effects. Since PWV is BP-dependent, a further analysis with the addition of mean BP (or alternatively systolic and diastolic BP) to the fully adjusted model was performed, to assess the potential contribution to BP on any observed PWV association with COVID status. Since there is some evidence of age and sex differences in susceptibility and effects of COVID, we tested interactions between COVID groups and sex in models, with the intention of performing stratified analysis if these were significant ($P < .05$).

Further sensitivity analyses were performed. First, we added being a healthcare professional as random factor. Second, we replaced the variable 'country income level' with the variable 'country' as random effect. Third, since criteria for admission to ICU could differ between hospitals and with time (e.g. related to ICU capacity), we repeated the analysis by grouping COVID+ patients hospitalized or hospitalized into ICUs, into a single category. Models including also ethnicity and HR as fixed effect covariates were performed. To check whether the relationship between PWV and COVID-19 severity was linear, we included in the model COVID group as a numerically ordered variable in terms of severity, rather than an unordered categorical variable. Finally, since the COVID− group resulted to differ significantly from the COVID+ hospitalized and ICU groups, especially in terms of age, sex and CV risk factors, we created a control group matched for age, sex, BMI, smoking, established CV disease, treated hypertension and diabetes with the CARTESIAN participants, but recruited before 2020, in the pre-COVID era. This historical control group has been extracted from the Austrian population-based LEAD study.[21] The R package MatchIt! was used.

In COVID+ patients, the impact of disease characteristics such as vaccination status and persistent symptoms at Visit 1, as well as the impact of CV drugs was explored.

Furthermore, in COVID+ patients, PWV differences within V1 and V2, taking place at 6 ± 3 months and 12 ± 3 months after COVID-19, were investigated by hierarchical mixed linear regression modelling analysis, adding ID as random factor and visit number as fixed factor. Adjusted and non-adjusted analyses were performed.

Since previous literature showed prognostic value for estimated PWV (ePWV) in COVID-19,[22] we also calculated ePWV according to the formula proposed in[23] and evaluated agreement with measured PWV by Bland-Altman analysis as well as association between ePWV and COVID status by hierarchical mixed linear regression modelling analysis.

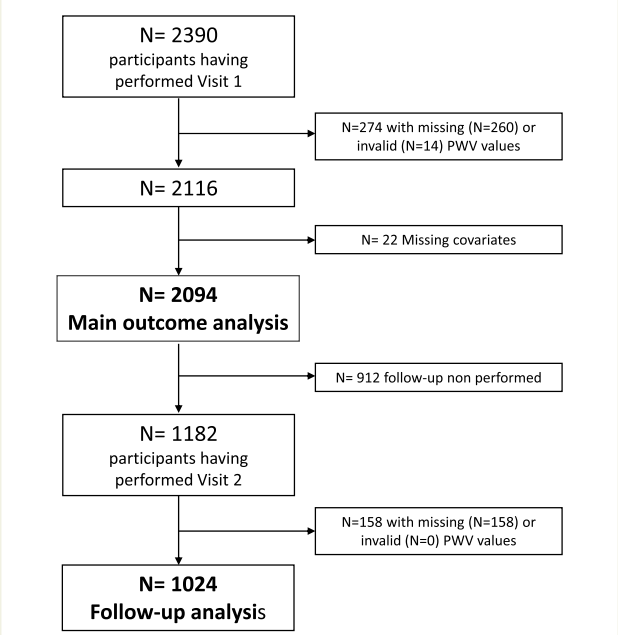


Figure 1 Study population flowchart of the CARTESIAN study. BP, blood pressure; PWV, pulse wave velocity

Results

Clinical and vascular characteristics of the study population

A diagram describing the study population flowchart is presented in *Figure 1*. Clinical characteristics of the overall study population, as well as differences between disease groups, are shown in *Table 1*. As expected, patients in the hospitalized (in medicine unit and in ICU) COVID+ groups were older, more frequently men, and had a higher burden of CV risk factors and disease compared with non-hospitalized COVID+ patients and COVID− controls. Non-hospitalized COVID+ had a substantially similar CV risk profile compared with COVID− controls.

Vascular characteristics of the study population are described in *Table 2*. The most used PWV measuring device was the Sphygmocor device (tonometric or oscillometric), accounting for 92% of the measurements. Unadjusted carotid-femoral PWV was higher in the non-hospitalized COVID+ patients and further higher in hospitalized COVID+ patients (either in hospital or ICU) compared with COVID− controls. Central and brachial BP and AIx differences showed broadly similar patterns to differences in PWV between groups.

Relevant sex differences in clinical and vascular characteristics, are shown in Supplementary data online, *Tables S1* and *S2*. Women were younger, more likely to be healthcare professionals, and had a lower burden of CV risk factors than men. Furthermore, they showed lower PWV, and higher AIx compared with men.

Carotid-femoral PWV in COVID-19 patients: hierarchical linear modelling analysis and sex-stratified analysis

Results for PWV in the overall population are shown in *Table 3*. The three COVID+ groups showed a significantly higher PWV than COVID− controls; differences between groups were significant after

Table 1 Demographic characteristics of the study population

Parameter	Control (Group 1) ($n = 391$)	COVID-19 with no hospitalisation (Group 2) ($n = 828$)	COVID-19 with hospitalisation (Group 3) ($n = 729$)	COVID-19 with ICU hospitalisation (Group 4) ($n = 146$)	Overall ($n = 2094$)	*P*-value
Age (years)	42.2 (32.3–54.3)	44.9 (34.4–56.2)	57.9 (50.1–67.4)*#	57.9 (49.8–65.0)*#	51.1 (38.7–60.6)	<.001
Sex (% Men)	44.5	38.6	63.6	71.9	50.8	<.001
Height (cm)	170 (163–177)	169 (163–177)	170 (164–177)	173 (166–180)*#^	170 (163–177)	<.001
Weight (Kg)	73 (60–85)	75 (65–88)*	81 (72–93)*#	85 (78–100)*#	78 (66–90)	<.001
BMI (Kg/m^2)	24.9 (22.3–28.2)	26.0 (23.1–29.4)*	28.0 (25.2–31.2)*#	29.1 (25.5–32.0)*#^	26.8 (23.7–30.1)	<.001
Systolic BP (mmHg)	119 (109–130)	123 (112–132)*	133 (123–144)*#	131 (122–141)*#	126 (115–138)	<.001
Diastolic BP (mmHg)	73 (66–80)	76 (69–83)*	80 (74–87)*#	79 (74–87)*#	77 (70–84)	<.001
Mean BP (mmHg)	89 (82–95)	91 (85–99)*	98 (91–105)*#	97 (91–105)*#	93 (86–101)	<.001
HR (bpm)	70.5 (62.4–80.4)	68 (61.5–76)*^	70 (63–78)	70.8 (63.2–79)	69.4 (72.4–77.7)	.002
Hypertension (%)	19.2	21.1	41.8	36.3	29.0	<.001
Diabetes (%)	2.30	7.37	18.8	23.3	11.5	<.001
Current Smoking (%)	12.5	11.3	3.29	0.68	8.02	<.001
Dyslipidemia (%)	12.0	20.5	28.4	33.6	22.6	<.001
Established Cardiovascular disease (%)	3.32	4.59	8.23	10.27	6.02	<.001
BP-lowering drug use (%)	16.6	19.0	31.3	28.8	23.5	<.001
Lipid-lowering drug use (%)	8.44	9.78	19.6	22.6	13.8	<.001
Glucose-lowering drug use (%)	2.81	5.80	14.1	16.4	8.88	<.001
Working as a healthcare professional (%)	40.7	26.8	7.27	7.53	21.2	<.001
Living in a Low-medium income country (%)	2.05	28.6	5.35	4.79	13.9	<.001
Ethnicity (%)						
Caucasian	89.5	77.7	91.4	89.7	85.5	
Asian	3.33	0.85	1.54	1.37	1.59	
Black	3.08	1.09	1.54	3.42	1.78	
Latin-American	1.54	9.82	1.82	2.05	4.97	
Middle East/North African	0.26	9.94	3.09	2.05	5.21	
Other	2.31	0.61	0.56	1.37	0.96	

Kruskal–wallis test with Bonferroni correction for multiple comparisons was used to compare the continuous variables and data is expressed as median (IQR). Chi square tests were used for categorical variables and data is expressed as percentages. Statistically significant difference from *—Group 1, #—Group 2, ^—Group 3.

adjustment for random effects variables, age and sex, as well as smoking, established CV disease, BMI, treated hypertension and diabetes. Adjusted PWV was higher by a similar magnitude (around +0.4 m/s compared with COVID− controls) in the three COVID+ groups. Differences remained significant after further adjustment for either mean BP or systolic and diastolic BP (*Table 3*).

A significant sex × group interaction was demonstrated in non-hospitalized COVID+ and those hospitalized in ICU, with borderline *P*-value for hospitalized COVID+; thus, a sex-stratified analysis was performed. The results of the adjusted models in men and women are shown in *Table 4* and *Figure 2*. COVID+ women showed a significantly higher PWV compared with COVID− women regardless of disease severity. Non-hospitalized COVID+ patients and those hospitalized in medicine units showed a similarly elevated PWV (+0.55 and 0.60 m/s), whereas in COVID+ women hospitalized in ICU, PWV difference was double (+1.09 m/s). In contrast, no difference between COVID+ and COVID− men was found. Results of sex-stratified analysis were substantially similar after further adjustment for mean BP (see Supplementary data online, *Table S3*). No significant interaction between disease group and presence of established CV disease (*P* for interaction .803, 0388 and .693 for non-hospitalized COVID+, hospitalized and ICU COVID+ respectively), age tertiles, or smoking was found (see Supplementary data online, *Figure S1*).

Table 2 Vascular characteristics of the study population

Parameter	Control (Group 1) (*n* = 391)	COVID-19 with no hospitalisation (Group 2) (*n* = 828)	COVID-19 with hospitalisation (Group 3) (*n* = 729)	COVID-19 with ICU hospitalisation (Group 4) (*n* = 146)	Overall (*n* = 2094)	*P*-value
PWV device						<.001
CVMS	72.1	46.4	70.1	84.9	62.1	
XCEL	9.97	46.4	25.8	10.9	29.9	
Other	17.9	7.25	4.12	4.11	7.93	
PWV (m/sec)	6.59 (5.25–7.86)	6.90 (6.00–8.00)*	7.90 (6.82–9.40)*#	7.98 (7.07–9.24)*#	7.22 (6.24–8.52)	<.001
Aortic Systolic BP (mmHg)	107 (97–116) *(n = 388)*	113 (103–124)* *(n = 809)*	123 (112–133)*# *(n = 603)*	120 (112–131)*# *(n = 137)*	115 (104–127) *(n = 1937)*	<.001
Aortic Diastolic BP (mmHg)	73 (67–81) *(n = 388)*	77 (70–84)* *(n = 806)*	80 (73–87)*# *(n = 604)*	81 (74–88)*# *(n = 137)*	77 (71–85) *(n = 1935)*	<.001
Aortic PP (mmHg)	32 (26–40) *(n = 388)*	35 (29–43)* *(n = 805)*	41 (34–51)*# *(n = 602)*	38 (34–46)*# *(n = 137)*	37 (30–46) *(n = 1932)*	<.001
Augmentation Index (%)	19.7 (8.67–30.0) *(n = 387)*	24.6 (14.4–34.0)* *(n = 806)*	24.0 (13.0–32.7)* *(n = 588)*	23.7 (15.7–31.0) *(n = 137)*	23.2 (12.7–32.4) *(n = 1918)*	<.001

Kruskal–wallis test with bonferrni correction for multiple comparisons was used to compare the continous variables and data is expressed as median (IQR). Chi square tests were used for categorical variables and data is expressed as percentages. Statistically significant difference from *—Group 1, #—Group 2.

Table 3 Hierarchical linear modelling analysis showing PWV differences between disease groups

Model	Variable	COVID-	Non-hospitalized COVID+	Hospitalized COVID+	ICU COVID+
Unadjusted	Mean (95% CI)	6.53 (6.10; 6.97)	7.06 (6.53; 7.60)	8.22 (7.73; 8.71)	8.17 (7.73; 8.61)
	Difference		+ 0.53 m/s	+1.69 m/s	+1.64 m/s
	P-value		<.001	<.001	<.001
Adjusted for age and sex	Adjusted mean (95% CI)	7.17 (6.89; 7.46)	7.57 (7.20; 7.95)	7.56 (7.21; 7.92)	7.59 (7.29; 7.89)
	difference		+ 0.40 m/s	+0.39 m/s	+0.42 m/s
	P-value		<.001	<.001	<.001
Adjusted for age, sex, smoking, established CV disease, BMI, diabetes, anti-HT drugs	Adjusted mean (95% CI)	7.53 (7.09; 7.97)	7.95 (7.53; 8.36)	7.90 (7.47; 8.33)	7.93 (7.46; 8.40)
	difference		+ 0.41 m/s	+0.37 m/s	+0.40 m/s
	P-value		<.001	.001	.003
Adjusted for age, sex, smoking, established CV disease, BMI, diabetes, anti-HT drugs, mean BP	Adjusted mean (95% CI)	7.70 (7.18; 8.22)	8.04 (7.53; 8.56)	7.90 (7.39; 8.42)	7.95 (7.42; 8.48)
	difference		+ 0.34 m/s	+0.20 m/s	+0.25 m/s
	P-value		<.001	.012	.042
Adjusted for age, sex, smoking, established CV disease, BMI, diabetes, anti-HT drugs, systolic and diastolic BP	Adjusted mean (95% CI)	7.68 (7.11; 8.26)	8.04 (7.46; 8.62)	7.90 (7.32; 8.48)	7.97 (7.39; 8.56)
	difference		+ 0.36 m/s	+0.22 m/s	+0.29 m/s
	P-value		<.001	.009	.026

Models adjusted for fixed factors: age, BMI, smoking, established CV disease, diabetes, anti-HT drugs, mean BP; random factors: device type, country income level.

Table 4 Hierarchical linear modelling analysis showing PWV differences between disease groups in men and women

Sex group	Variable	COVID−	Non-hospitalized COVID+	Hospitalized COVID+	ICU COVID+
Women	Mean (95% CI)	6.80 (6.34; 7.26)	7.36 (6.94; 7.77)	7.40 (6.94; 7.77)	7.89 (7.30; 8.48)
	Difference		+ 0.55 m/s	+0.60 m/s	+1.09 m/s
	P-value		<.001	<.001	<.001
Men	Adjusted mean (95% CI)	8.30 (7.72; 8.89)	8.46 (7.93; 9.00)	8.38 (7.81; 8.94)	8.24 (7.63; 8.86)
	Difference		+ 0.16 m/s	+ 0.07 m/s	−0.06 m/s
	P-value		.212	.556	.791
	P-value for interaction group × sex		.025	.099	.005

Models adjusted for fixed factors: age, BMI, smoking, established CV disease, diabetes, anti-HT drugs; random factors: device type, country income level.

Sex group	Variable	COVID−	Non-hospitalized COVID+	Hospitalized COVID+	ICU COVID+
Women	Mean (95% CI)	7.02 (6.54; 7.50)	7.44 (6.99; 7.89)	7.38 (6.90; 7.86)	7.91 (7.31; 8.50)
	Difference		+ 0.42 m/s	+0.36 m/s	+0.89 m/s
	P-value		<.001	.003	<.001
Men	Adjusted mean (95% CI)	8.35 (7.67; 9.04)	8.52 (7.87; 9.18)	8.33 (7.65; 9.00)	8.19 (7.49; 8.89)
	Difference		+ 0.16 m/s	− 0.03 m/s	−0.16 m/s
	P-value		.093	.871	.508
	P-value for interaction group × sex		.103	.425	.013

Models adjusted for fixed factors: age, BMI, smoking, established CV disease, diabetes, anti-HT drugs, mean BP; random factors: device type, country income level.

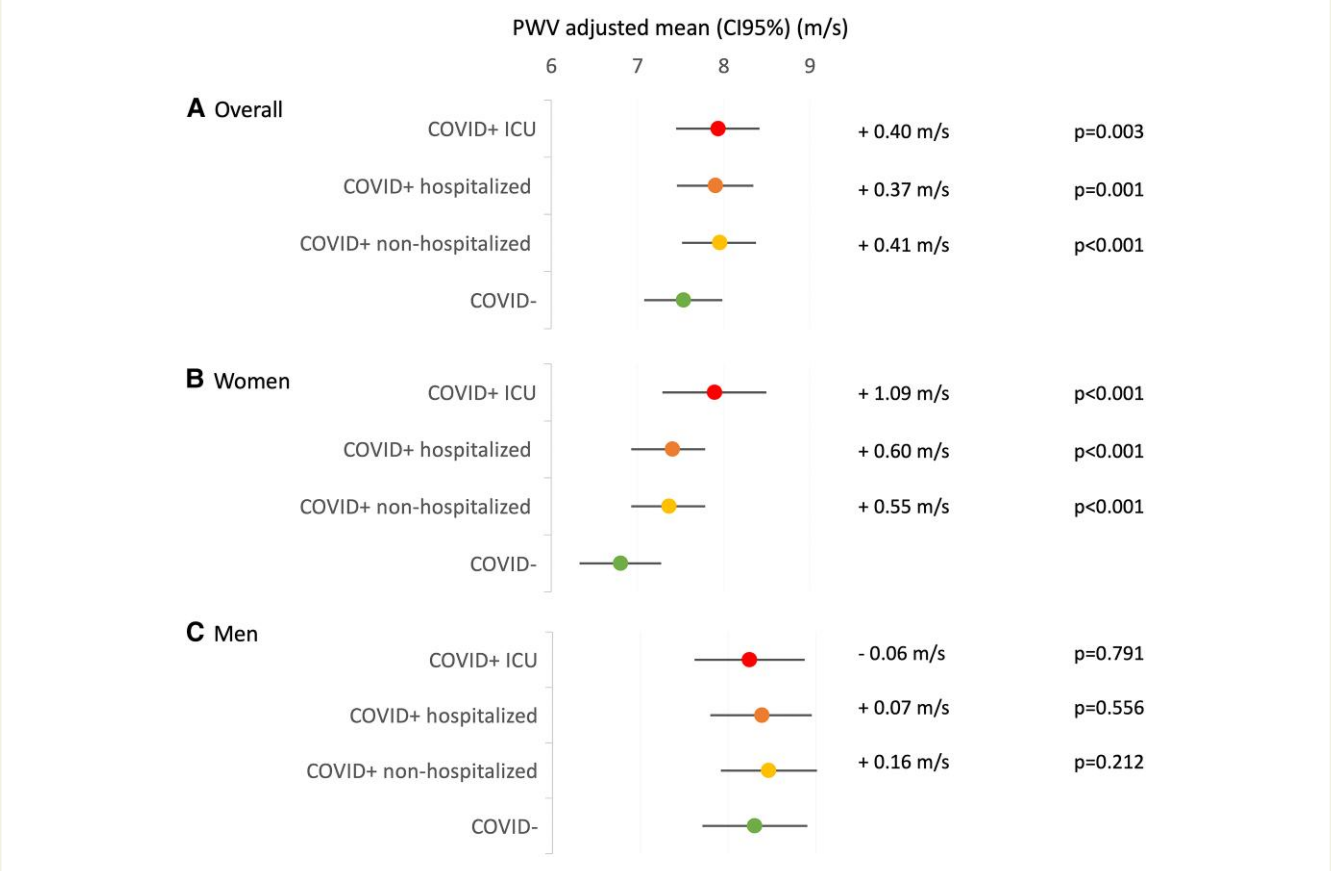


Figure 2 PWV differences between disease groups in the overall population (A), in women (B) and in men (C). Hierarchical linear models are adjusted for fixed factors: age, BMI, diabetes, anti-HT drugs, smoking, established CV disease; random factors: device type, country income level. ICU, intensive care unit; PWV, pulse wave velocity

Sensitivity analyses

Adding healthcare professional status as random factor in the fully adjusted model in men and women did not substantially change the results (see Supplementary data online, *Table S4*). The same was true, when replacing the variable 'country income level' with the variable 'country' as random effect (see Supplementary data online, *Table S5*) and when grouping the COVID+ patients hospitalized in medicine and ICU in a single category (see Supplementary data online, *Table S6*). Adding heart rate (see Supplementary data online, *Table S7*) or ethnicity (see Supplementary data online, *Table S8*) as fixed effects in the final model did not materially change the results. Estimated PWV showed 1.1 m/s difference compared with measured PWV (see Supplementary data online, *Figure S2*) and was not significantly different between COVID− and COVID+ groups in the fully adjusted model (see Supplementary data online, *Table S9*).

Comparison with historical control cohort

Clinical characteristics of the overall LEAD population are described elsewhere.[21] PWV was higher in CARTESIAN COVID+ participants compared with the matched LEAD participants, whereas no difference was found between CARTESIAN COVID− participants and matched LEAD participants (see Supplementary data online, *Table S10*). Similar results were found when restricting the CARTESIAN population to those recruited in European countries (see Supplementary data online, *Table S11*).

Determinants of PWV in subgroups

Fully adjusted models were run in the overall population, in men and women separately (see Supplementary data online, *Table S12*) and in COVID−, non-hospitalized and hospitalized COVID+ (*Table 5*). Whereas traditional CV risk factors were similarly associated with PWV in all disease groups, Asian, Latin-American and other ethnicities had lower PWV values compared with Caucasians in the COVID− but not in the COVID+ groups.

Disease variables in COVID+ patients are shown in Supplementary data online, *Table S13*. Among COVID+ patients, 10.0% had been vaccinated with at least one dose at the time of Visit 1, mostly with Pfizer/BioNTech vaccine. In the sex-stratified hierarchical linear modelling analysis, fully adjusted and including vaccination status at Visit 1 as a fixed effect, vaccinated women had significantly lower PWV than unvaccinated women [adjusted PWV 7.35 (95% CI 6.85; 7.85) vs. 7.71 (95% CI 7.26; 8.16) m/s, $P = .027$, adjusted difference −0.36 m/s]. In men, the difference between vaccinated and unvaccinated COVID+ patients was not significant [adjusted PWV 8.42 (95% CI 7.79; 9.04) vs. 8.65 (95% CI 8.21; 9.09) m/s, $P = .224$, adjusted difference −0.23 m/s] (*Figure 3*).

Among COVID+ patients, 42.2% complained of persistent symptoms after COVID-19 at the time of Visit 1. The most common symptoms were fatigue, dyspnoea and myalgias (see Supplementary data online, *Table S13*). Women with persistent COVID-19 symptoms at Visit 1 had significantly higher PWV than those who fully recovered [adjusted PWV 7.52 (95% CI 7.09; 7.96) vs. 7.13 (95% CI 6.67; 7.59) m/s, $P < .001$, adjusted difference 0.39 m/s]. In men, difference between COVID+ patients with or without persistent symptoms was not significant [adjusted PWV 8.50 (95% CI 7.94; 9.06) vs. 8.43 (95% CI 7.87; 9.00 m/s) m/s, $P = .563$, adjusted difference 0.07 m/s] (*Figure 3*).

Finally, we explored whether the chronic use of vasculoprotective drugs influenced arterial stiffness in our population. Use of lipid-lowering

Table 5 Determinants of PWV according to COVID groups

	COVID−			Non-hospitalized COVID +			Hospitalized COVID + (Hospital + ICU)		
	Beta-coeff.	**SE**	***P*-value**	**Beta-coeff.**	**SE**	***P*-value**	**Beta-coeff.**	**SE**	***P*-value**
(Intercept)	1.974	0.824	.017	0.659	0.474	.165	−0.172	1.002	.864
Age	**0.067**	**0.006**	**<.001**	**0.06**	**0.003**	**<.001**	**0.073**	**0.007**	**<.001**
Female sex	**−0.678**	**0.16**	**<.001**	**−0.4**	**0.084**	**<.001**	**−0.434**	**0.167**	**.01**
BMI	−0.017	0.017	.296	**−0.02**	**0.009**	**.027**	**−0.051**	**0.017**	**.003**
Diabetes	1.26	0.492	.011	**0.407**	**0.164**	**.013**	**1.016**	**0.205**	**<.001**
BP-lowering drug use	**0.762**	**0.218**	**.001**	**0.486**	**0.118**	**<.001**	0.119	0.182	.513
Smoking (reference—never)									
−Ex	0.016	0.184	.929	−0.112	0.102	.275	−0.052	0.175	.768
−Current	0.28	0.229	.221	0.054	0.128	.675	−0.233	0.523	.656
Established CV disease	−0.36	0.408	.379	−0.029	0.198	.885	0.135	0.328	.68
Heart rate	0.01	0.007	.132	**0.007**	**0.004**	**.094**	**0.018**	**0.007**	**.013**
Mean BP	**0.021**	**0.008**	**.007**	**0.042**	**0.004**	**<.001**	**0.039**	**0.007**	**<.001**
Ethnicity (reference -caucasian)									
−Asian	**−1.773**	**0.399**	**<.001**	−0.553	0.429	0.198	0.77	0.547	0.16
−Black	0.583	0.421	.167	−0.578	0.392	0.141	0.874	0.521	0.094
−Latin-American	**−1.221**	**0.618**	**.049**	−0.09	0.169	0.594	0.317	0.638	0.619
−Middle East/North Africa	1.093	1.377	.428	0.437	0.249	0.079	−0.019	0.572	0.973
−Other	**−1.235**	**0.471**	**.009**	−0.68	0.514	0.186	0.55	0.831	0.509

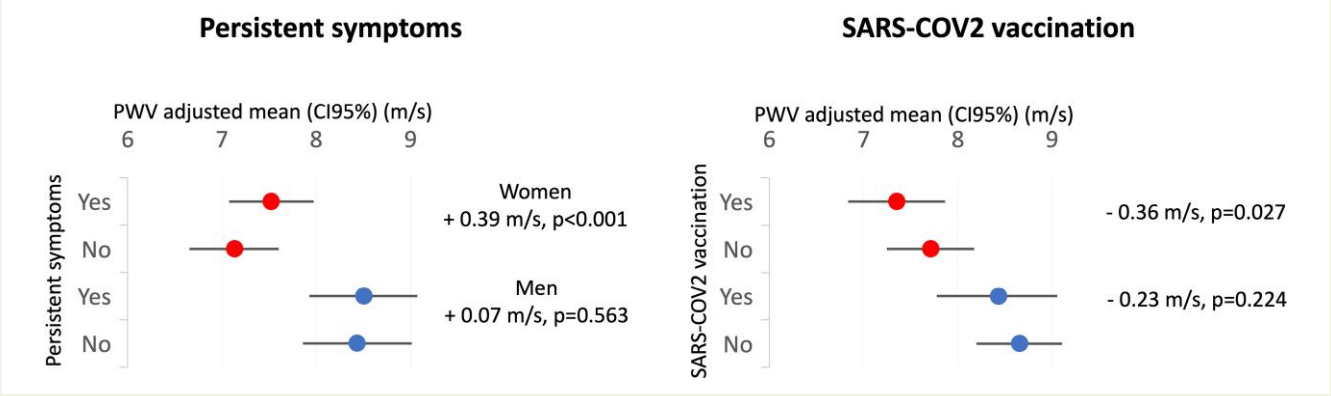


Figure 3 Disease-specific determinants of PWV in men and women. Hierarchical linear models are adjusted for fixed factors: age, BMI, diabetes, anti-HT drugs, smoking, established CV disease; random factors: device type, country income level. PWV, pulse wave velocity

drugs (in the overall population), renin-angiotensin system blockers (in the subset of treated hypertensive patients) or metformin (in the subset of treated diabetic patients), was not associated with a lower PWV either in women or in men when added to the fully adjusted model (data not shown).

Long-term persistence of elevated PWV after COVID-19

In a subgroup of 1024 participants vascular measurements were repeated during follow-up. Median delay between Visit 1 and Visit 2 was 314 (IQR 232–352) days. Clinical and vascular characteristics of this population are shown in Supplementary data online, *Tables S14* and *S15*, whereas disease characteristics in COVID+ patients were shown in Supplementary data online, *Table S16*. A significant group × visit interaction for all 3 COVID+ groups compared with the COVID− group has been found in a repeated measures mixed-model analysis adjusted for confounders, revealing a stable or improved PWV over time in the COVID+ groups, whereas a PWV increase was shown in the COVID− group (*Figure 4*, *Table 6*). The prevalence of COVID-19-related persistent symptoms was significantly reduced from 46.0% in V1 to 37.6% in V2, and the prevalence of vaccinated people increased from 10.4% in V1 to 72.2% in V2. Whereas persistent symptoms were no longer associated with PWV when added to the fully adjusted repeated measures mixed-model, the significant association between vaccination and lower PWV was confirmed, especially in hospitalized COVID+ group (data not shown). In seven participants recruited in the COVID− group and performing PWV at Visit 1 and 2, a positive PCR test was reported in the time period between the two visits. For all seven participants, we observed an increase in PWV values after the infection (see Supplementary data online, *Figure S3*). Considering the expected probability of an increase in PWV during the second visit of 0.58, and a binomial distribution, the probability of observing this increase in all seven participants by chance is very low ($P = .022$), indicating a significant effect of infection on PWV increase.

Discussion

The CARTESIAN study is a large international, multicentric study investigating long-term consequences of COVID-19 on biomarkers of vascular ageing. In this paper, reporting the results of the main outcome variable, carotid-femoral PWV, we demonstrated an association between COVID-19 and elevated arterial stiffness. This association is independent of measured confounders and COVID-19 severity and is due only in part to BP elevation. Elevated arterial stiffness is partially attenuated in the long term, as shown by 12-month follow-up data. Notably, there is evidence of effect modification by sex, indicating that COVID-19 associated vascular ageing is more marked in women. PWV elevation was evident even in non-hospitalized COVID+, and similar in magnitude to that seen in COVID+ women hospitalized in medicine units (around +0.5 m/s compared with COVID− women). PWV elevation was even larger in COVID+ women hospitalized in ICU (>1 m/s). We were able to investigate factors related to accelerated vascular ageing in female COVID-19-survivors: vaccination was associated with lower PWV, whereas presence of persistent symptoms was associated with higher PWV. In contrast, no difference between COVID+ and COVID− groups was found in men (*Structured Graphical Abstract*). Previous studies have reported a higher mortality due to COVID-19 in men than women[24,25] which may have an impact on the population distribution with a potential survivor bias, and thus attenuated the difference in PWV between groups in men.

Increasing knowledge is accumulating about COVID-19-induced vascular damage. An early autopsy study reported viral inclusion structures in endothelial cells from different organs, together with signs of endotheliitis and apoptotic bodies.[26] Endothelial SARS-CoV-2 penetration has consequences on endothelial function: in vascularized human lung-on-chip models, although endothelial infection is unproductive, it leads to reduced ACE2 mRNA, progressive loss of barrier integrity, and a pro-coagulatory microenvironment. Viral RNA persists in endothelial cells, generating a persistent inflammatory response, even in the absence of immune cells,[27] thus constituting a molecular basis for development of vascular damage.[28] Biomarkers of endothelial activation are persistently altered 2 months after acute COVID-19.[29] Aortic inflammation is increased in the early post-COVID phase in patients with severe or critical COVID-19; although it largely resolves over time, it may trigger further fibrotic changes inducing the long-lasting phenomenon of arterial stiffening.[30] Some initial observations in small samples had already shown sub-acute vascular alterations (endothelial dysfunction and arterial stiffness) among young adults 3–4 weeks after mild SARS-CoV-2 infection.[31] Later, few small single-centre studies reported increased arterial stiffness up to 6 months after an acute COVID-19 infection.[32–34] Two of these cohorts[32,34] agreed to contribute with their data to the CARTESIAN consortium. However, the

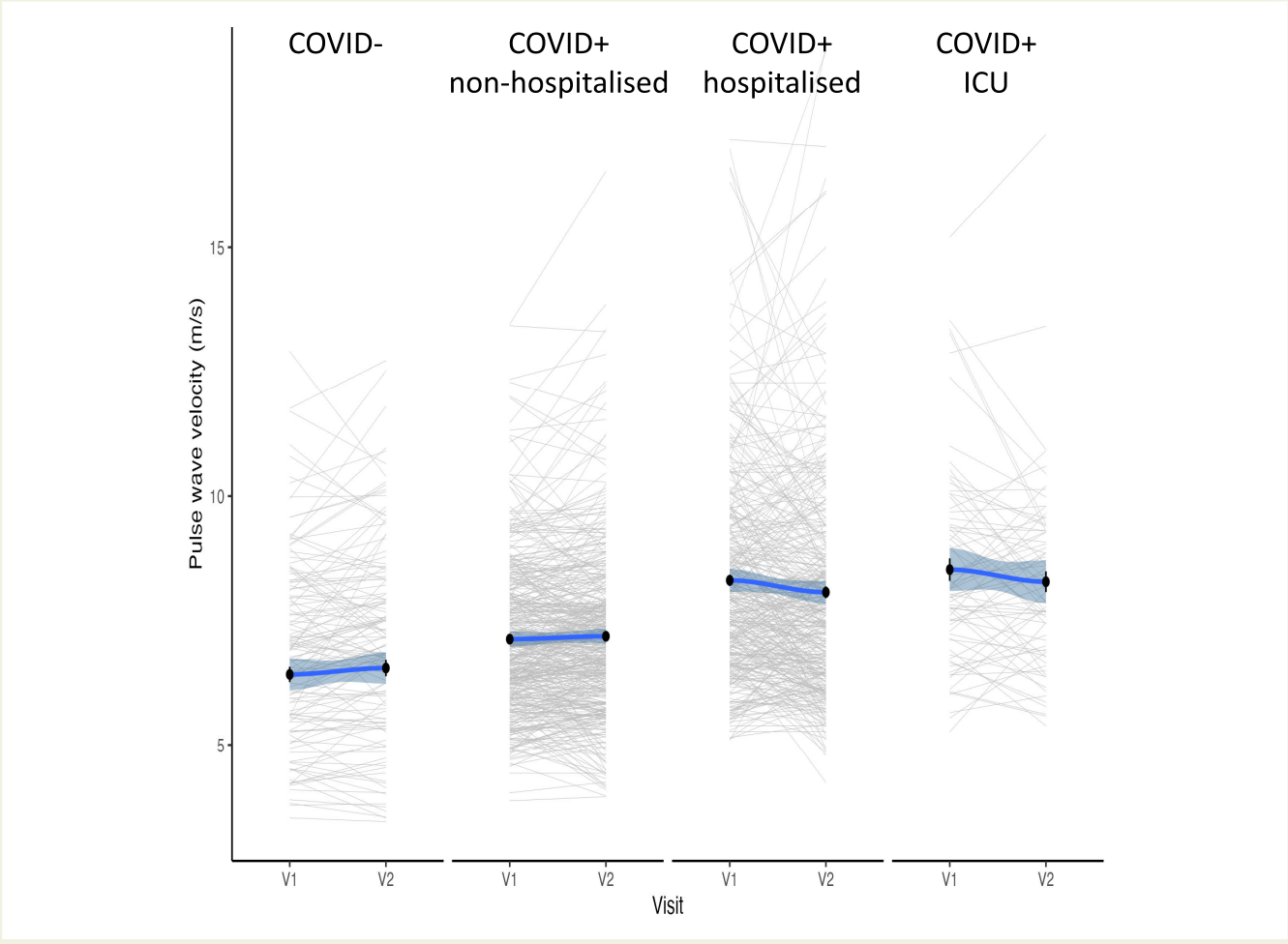


Figure 4 Individual and groups averaged PWV changes between Visit 1 and Visit 2. Unadjusted values. ICU, intensive care unit; PWV, pulse wave velocity

Table 6 Hierarchical linear modelling analysis showing PWV differences between Visit 1 and Visit 2 according to COVID status groups

	COVID-	Non-hospitalized COVID+	Hospitalized COVID+	ICU COVID+
Visit 1	6.96 (6.64–7.27)	7.14 (6.96–7.32)	8.31 (8.11–8.51)	8.52 (8.10–8.95)
Visit 2	7.08 (6.77–7.40)	7.20 (7.02–7.38)	8.07 (7.87–8.27)	8.28 (7.86–8.70)
***P* for interaction group × visit**		.539	.002	.031

Model adjusted for fixed factors: visit, interaction disease group × visit; random factors: subject ID.

	COVID−	Non-hospitalized COVID+	Hospitalized COVID+	ICU COVID+
Visit 1	7.23 (4.38–10.08)	7.93 (4.40–11.47)	7.54 (4.25–10.84)	7.57 (5.02–10.13)
Visit 2	7.50 (4.79–10.22)	7.91 (4.41–11.42)	7.23 (3.96–10.50)	7.35 (4.93–9.76)
***P* for interaction group × visit**		.048	<.001	.018

Model adjusted for fixed factors: visit, age, sex BMI, smoking, established CV disease, diabetes, anti-HT drugs; random factors: subject ID, device type, country income level.

CARTESIAN study is the first study adequately powered to demonstrate the extent of COVID-19-induced vascular ageing and the relationship with disease severity, independent of CV risk factor burden. Indeed, it is well known that age and CV risk factors, such as diabetes or obesity, are associated with worse COVID-19 outcomes, thus suggesting the existence of a bidirectional relationship between CV disease and COVID-19.[35,36] Our results also indicate the association between vascular ageing and COVID-19 is only partly mediated by BP values.

A number of population studies found an increase in BP values during the COVID-19 pandemic, which were more marked in women than in men[37]; hypertension diagnosis was also increased after COVID-19 regardless of COVID-19 severity.[1,38]

To our knowledge, this is the first study demonstrating that the association between COVID-19 and vascular ageing is modified by sex. Despite general lack of sex-disaggregated data (https://globalhealth5050.org/the-sex-gender-and-covid-19-project/), sex differences in COVID-19 outcomes are well known.[39] As we observed also in our cohort, men are more susceptible to severe acute COVID-19 illness,[24] even after adjusting for lower prevalence of pre-existing risk factors in women.[40] However, cohort studies have consistently reported that women have greater risk for long COVID.[41] The CARTESIAN study demonstrated that COVID-19 is associated with arterial stiffening especially in women, thus adding a new dimension to long COVID syndrome definition. Indeed, in our study the presence of persistent symptoms 6 months after COVID-19 infection was significantly associated with increased PWV in women, for any degree of disease severity and regardless of other confounders. Mechanisms underlying long COVID are only partially elucidated.[42,43] Persistent inflammation and viral persistence after acute infection[44] may be involved in both long COVID symptoms and accelerated vascular ageing. Differences in immune system function between females and males could be an important driver of sex differences in long COVID-19 syndrome. Females mount more rapid and robust innate and adaptive immune responses, which can protect them from initial infection and severity. However, this same difference can increase susceptibility to prolonged autoimmune-related diseases.[45,46]

Interestingly, PWV elevation was evident even in non-hospitalized COVID+, what has been called mild COVID-19, at a similar degree of COVID+ women hospitalized in general wards. The magnitude of COVID-19-induced accelerated vascular ageing in these two disease groups is clinically relevant, around +0.5 m/s compared with COVID− women: if we compare this value with PWV reference values and meta-analysis of longitudinal studies, for a 60-year old person with normal BP a +0.5 m/s PWV roughly corresponds to +5 years of vascular ageing and +3% increased risk for CV events.[9,47] This is in line with results from large electronic medical registries showed an increased incidence of CV conditions such as hypertension, diabetes and heart failure even in mild COVID-19.[1] However, it is important to note that most CARTESIAN participants were enrolled during the first COVID-19 waves, when overwhelmed healthcare systems were not able to hospitalize all patients that might have required it, thus lack of hospitalisation might not necessarily be a good sign of lower severity. Interestingly, PWV elevation was even larger in COVID+ women hospitalized in ICU (>1 m/s compared with negative controls), roughly corresponding to +7.5 years of vascular ageing and +5.5% risk for CV events. Indeed, other studies have demonstrated that COVID-19 CV burden increases with increasing disease severity.[1] Since severe systemic infections, such as hospitalized pneumonia[48] and sepsis[49] are associated with increased long-term risk of CV events, the greater impact of COVID-19 on PWV seen in ICU patients may not be specific to COVID-19.

Finally, 12-month follow-up data suggest that COVID-19-induced vascular ageing is at least in part reversible in the long term. The slight increase in PWV seen in the COVID-19 group could be attributed partly to normal ageing, but also to a possible asymptomatic or undiagnosed subsequent COVID-19 infection in these patients.

The CARTESIAN study allowed us investigating the possible determinants of vascular stiffness in COVID+ and COVID− participants. Interestingly, we found relevant differences in the impact of ethnicity in COVID+ and COVID− participants: Asian, Latin-American and other ethnicities had lower PWV values compared with Caucasians in the COVID− but not in the COVID+ groups suggesting that COVID-19 offsets more favourable vascular ageing profiles associated with certain ethnicities. Furthermore, a lower PWV was found in vaccinated compared with unvaccinated women, both in the 6-month and 12-month analysis, confirming preliminary results.[50] This finding is in line with reduced incidence of CV events demonstrated in the N3C cohort after vaccination.[51] Interestingly, COVID-19 vaccination has been reported to reduce the severity of symptoms in people with long COVID.[52] An increase in antibody titres or elimination of viral reservoirs could contribute to the reduction of accelerated vascular ageing after vaccination,[51] though underlying mechanisms are largely unknown. However, given the observational study design, we cannot exclude confounding by indication, a bias related to intrinsic differences between vaccinated and non-vaccinated individuals.

Strengths and limitations

Strengths of this study are the large sample size, the widespread recruitment worldwide, the use of a standardized, gold-standard methodology for arterial stiffness measurement, the presence of follow-up arterial stiffness evaluations. We would also like to acknowledge a number of limitations of our study. First, since the cohort has been recruited 6 months after COVID-19 infection, it is potentially subjected to survival bias; for the same reason, it is not possible to firmly exclude that early vascular ageing was pre-existing to COVID-19. However, it is important to mention that accelerated vascular ageing induced by COVID-19 has been confirmed by small-sized pre-post studies[53,54] and by an exploratory subgroup analysis in 7 CARTESIAN participants. Furthermore, the 12-month follow-up data support the temporal relation between COVID-19 and PWV.

Second, the population sample study, though large and diverse in terms of geographical span, may be not representative of the general population, mostly due to constraints on recruiting during a pandemic. In particular, the control group is relatively small and is not adequately matched to the hospitalized COVID-19 subgroups: despite statistical adjustment, some unmeasured confounders can still impact on the analysis. Furthermore, due to lack of systematic serology testing, it is conceivable that a number of individuals who have experienced asymptomatic or mild COVID-19 have been included in the COVID− group.

However, comparison with an adequately matched population sample recruited before 2020 confirmed absence of relevant bias. Third, we cannot exclude residual confounding due to unmeasured factors that contribute either to risk of COVID-19 or to elevated PWV and that may have been incompletely controlled for in statistical models. This limitation is particularly relevant to the results related to vaccination, which should be interpreted with caution due to potential confounding by indication.

Conclusions

In conclusion, despite the acknowledged limitations intrinsic to the design of the study, our data indicate that COVID-19 infection is associated with mid-term and long-term accelerated vascular ageing, especially in women. Further studies are needed to confirm these findings with pre-post studies and to elucidate the effect of vaccination, as well as to demonstrate whether these preclinical alterations are associated with clinical CV events; whether newer SARS-CoV-2 variants are able to induce accelerated vascular ageing to the same extent, and whether reinfections[55] are associated with worse arterial stiffness.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Nothing to declare.

Data Availability

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author, who will submit the request to the CARTESIAN Scientific Committee.

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Ethical Approval

The CARTESIAN study was planned as a joint analysis of several national studies, using an identical protocol written by the Cartesian Scientific Committee. Approval by local Ethics Committee was obtained in each centre. Additional studies, with ethical clearance complying with the declaration of Helsinki and using similar techniques and protocols, were also included in the final analysis of the CARTESIAN study.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is Clinicaltrials.gov (NCT04558450).

Appendix

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